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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/724,538	SHOEMAKER ET AL.
	Examiner	Art Unit
	Frank W Lu	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-34,36,45,46,86-90,157-181,183,212,213,263-267 and 280-296* is/are pending in the application.

4a) Of the above claim(s) *46,88,212,213,266 and 267* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-34,36,45,86,87,89,90,157-181,183,263-265 and 280-296* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *01 April 2003* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *filed on 4/03*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on September 20, 2004 has been entered. The previous suspension has been released by the examiner. The claims pending in this application are claims 1, 4-34, 36, 45, 46, 86-90, 157-181, 183, 212, 213, 263-267, and 280-296 wherein claims 46, 88, 212, 213, 266, and 267 have been withdrawn due to species election. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on September 20, 2004.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 4-34, 36, 45, 86, 87, 89, 90, 157-181, 183, 263-265, 280-283, and 293-296 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 1 is rejected as vague and indefinite. Since the first part of the claim indicates measuring the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes while the second part of the claim indicates that said measuring comprises measuring the expression level of each of a plurality of different variants of said exon in one gene. Since a plurality of different variants are from one exon of one of a plurality of different genes, it is unclear how to measure the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality

of different genes by measuring a plurality of different variants from one exon of one of a plurality of different genes. Please clarify.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, 4-6, 10-12, 22-32, 34, 36, 45, 157-159, 170-179, 181, 183, 264, 280-285, and 289-292 are rejected under 35 U.S.C. 102(e) as being anticipated by Penn *et al.*, (WO 01/57252 A2, priority date: February 4, 2000).

The rejection below is made in view of the ambiguity on claim 1 (see above rejections under 35 USC 112, second paragraph).

Regarding claims 1, 10, and 157, since Penn *et al.*, teach a method of detecting alternatively spliced mRNA variants comprising: detecting variations, as among a plurality tissues or cell types, in the expression pattern of a plurality of a gene's exons, said expression pattern measured for each of said tissues or cell types by concurrent hybridization of a plurality of exon-specific probes to transcript-derived nucleic acids from said tissue or cell type, wherein each of said plurality of exon-specific probes includes a fragment of no more than one exon of a eukaryotic genome, said fragment selectively hybridizable at high stringency to an expressed gene, wherein said probes collectively include specifically hybridizable fragments of a plurality

of exons of at least one gene, wherein said genome has, on average, at least one intron per gene, and wherein said plurality of probes averages at least 100 bp in length, and wherein said plurality of exon-specific probes are disposed, prior to said hybridization, on a nucleic acid microarray (see page 110, claims 1 and 2, and abstract) and mRNA is used as a sample (see pages 50 and 93), and it is known that alternatively spliced mRNA variants are generated from using a different 3' or 5' splice junction of exons of pre-mRNA, Penn *et al.,* disclose measuring the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes (ie., a plurality of exons of at least one gene) in the genome of an organism from which said cell sample is derived, wherein at least one gene in said plurality of different genes has an exon having a plurality of different variants, and wherein said measuring comprises measuring the expression level of each of said plurality of different variants of said exon in said at least one gene, each of said plurality of different variants being a different splice form of said exon generated using a different 3' or 5' splice junction of said exon, thereby analyzing the exon expression of said cell sample as recited in claim 1, and disclose contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAs or nucleic acids, wherein said array comprises a plurality of polynucleotide probes of different nucleotide sequences (ie., a plurality of exon-specific probes) bound to different regions of a support, each of said different nucleotide sequences comprising a sequence complementary and hybridizable to a sequence in a different exon or multiexon of said cell sample, wherein said plurality of probes comprises probes that allow measurement of the expression levels of said plurality of different variants of said exon

and measuring levels of hybridization between said probes and said RNAs or nucleic acids as recited in claim 10, and disclose contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAS or nucleic acids, wherein said array comprises a plurality of polynucleotide probes of different nucleotide sequences (ie., a plurality of exon-specific probes) bound to different regions of a support, each of said different nucleotide sequences comprising a sequence complementary and hybridizable to a sequence in a different exon or multiexon in the genome of an organism from which said cell sample is derived, wherein said plurality of probes comprises probes that allow measurement of the expression levels of said plurality of different variants of said exon and measuring levels of hybridization between said probes and said RNAS or nucleic acids as recited in claim 157.

Regarding claims 284 and 285, since Penn *et al.*, teach a method of detecting alternatively spliced mRNA variants comprising: detecting variations, as among a plurality tissues or cell types, in the expression pattern of a plurality of a gene's exons, said expression pattern measured for each of said tissues or cell types by concurrent hybridization of a plurality of exon-specific probes to transcript-derived nucleic acids from said tissue or cell type, wherein each of said plurality of exon-specific probes includes a fragment of no more than one exon of a eukaryotic genome, said fragment selectively hybridizable at high stringency to an expressed gene, wherein said probes collectively include specifically hybridizable fragments of a plurality of exons of at least one gene, wherein said genome has, on average, at least one intron per gene, and wherein said plurality of probes averages at least 100 bp in length, and wherein said plurality of exon-specific probes are disposed, prior to said hybridization, on a nucleic acid microarray

(see page 110, claims 1 and 2, and abstract) and include intergenic and/or intronic material contiguous to the exon (see page 56, second paragraph) and mRNA is used as a sample (see pages 50 and 93), and it is known that alternatively spliced mRNA variants are generated from using a different 3' or 5' splice junction of exons of pre-mRNA, Penn *et al.,* disclose contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAs or nucleic acids, wherein said array comprises (i) one or more exon specific probes comprising different nucleotide sequences for each of a plurality of different genes in the genome of said organism, each of said different nucleotide sequences being complementary and hybridizable to a sequence within a different individual exon; and (ii) a variant junction probe (ie., the exon probes with intergenic and/or intronic material contiguous to the exon) for each of a plurality of different variants of at least one exon, each of said variants being a different splice form of said exon generated using a different 3' or 5' splice junction of said exon, and each of said variant junction probes being a probe specific to a junction region of said variant and an adjacent exon in a multiexon comprising said variant of said exon, each of said exon specific probes and variant junction probes being bound to a different region of a support, and measuring levels of hybridization between said probes and said RNAs or nucleic acids as recited in claim 284, and disclose contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAs or nucleic acids, wherein said array comprises a plurality of junction specific probes (ie., the exon probes with intergenic and/or intronic material contiguous to the

exon) comprising different nucleotide sequences for each of a plurality of different genes in the genome of said organism bound to different regions of a support, each of said different nucleotide sequences being complementary and hybridizable to a sequence spanning a junction region of a multiexon (ie., two exons), and wherein said plurality of junction specific probes comprises a variant junction probe for each of a plurality of different variants of at least one exon, each of said variants being a different splice form of said exon generated using a different 3' or 5' splice junction of said exon, and each of said variant junction probes being a probe specific to a junction region of said variant and an adjacent exon in a multiexon comprising said variant of said exon, and measuring levels of hybridization between said probes and said RNAs or nucleic acids as recited in claim 285.

Regarding claims 4-6, 11, 12, 158, and 159, since Penn *et al.,* teach to use their method for detecting different genes such as tubulin, actin, glyceraldehyde-3-phosphate dehydrogenase, a translation elongation factor 1a, and a DEAD-box homolog (see pages 101 and 102), Penn *et al.,* disclose that said plurality of different individual exons (ie., exons from tubulin, actin, glyceraldehyde-3-phosphate dehydrogenase, a translation elongation factor 1a, and a DEAD-box homolog) or different individual multiexons consists of at least 2-5 different exons or multiexons as recited in claims 4-6, 11, 12, 158, and 159.

Regarding claims 22-27, 169-174, and 289-292, Penn *et al.,* teach that each of said different nucleotide sequences consists of 10 to 1,000 nucleotides as recited in claims 22 and 169, each of said different nucleotide sequences consists of 15 to 600 nucleotides as recited in claims 23 and 170, each of said different nucleotide sequences consists of 15 to 200 nucleotides as recited in claims 24, 171 and 289, each of said different nucleotide sequences consists of 20 to

100 nucleotides as recited in claims 24, 172, and 290, and each of said different nucleotide sequences consists of 40 to 80 nucleotides as recited in claims 26, 175, and 291, and each of said different nucleotide sequences consists of 60 nucleotides as recited in claims 27, 174, and 292 (see page 47, second paragraph, page 54, third paragraph, and page 55, second paragraph).

Regarding claims 28, 29, 175, and 176, since Penn *et al.,* teach that the probes in the microarray are covalently linked to the substrate surface (see page 47, third paragraph), Penn *et al.,* disclose that at least one probe in said plurality of probes contains, in addition to said sequence complementary and hybridizable to a different exon or multiexon, linker sequences as recited in claims 28 and 175, said linker sequence comprises a linker sequence between said sequence complementary and hybridizable to a different exon or multiexon and said support as recited in claims 29 and 176.

Regarding claims 30 and 177, Penn *et al.,* teach that said linker sequence comprises a linker sequence between said sequence complementary and hybridizable to a different exon or multiexon and said support (see claim 19 in page 113).

Regarding claims 31, 32, 178, and 179, since the rejections on claims 1 and 157 are not based on different individual multiexons which is an optional limitation in claims 1 and 15 and claims 31, 32, 178, and 179 are used to further limit different individual multiexons, claims 31, 32, 178, and 179 are anticipated by Penn *et al.*.

Regarding claims 34 and 181, Penn *et al.,* teach that said array of polynucleotide probes further comprises control polynucleotide probes comprising sequences complementary and hybridizable to different introns of said plurality of genes in the genome of said organism.

Regarding claims 36 and 183, Penn *et al.,* teach that said expression levels are measured as abundance of mRNA transcripts (see column 49, third paragraph).

Regarding claims 45, Penn *et al.,* teach that said organism is a human (see page 31, third paragraph).

Regarding claim 264, Penn *et al.,* teach that said array of polynucleotide probes comprises variant junction probes, wherein each of said variant junction probes is specifically hybridizable to a sequence spanning the splice junction between a different variant of said exon having a plurality of different variants and an adjacent exon (see page 56, second paragraph).

Regarding claims 280-283, since claims 280-283 are identical to claims 23-27, claims 280-283 are anticipated by Penn *et al.*.

Therefore, Penn *et al.,* teach all limitations recited in claims 1, 4-6, 10-12, 22-32, 34, 36, 45, 157-159, 170-179, 181, 183, 264, 280-285, and 289-292.

7. Claims 7-9, 13, 160, and 286-288 are rejected under 35 U.S.C. 102(e) as being anticipated by Penn *et al.,* as applied to claims 1, 4-6, 10-12, 22-32, 34, 36, 45, 157-159, 170-179, 181, 183, 264, 280-285, and 289-292 above as evidence by Pardee *et al.,* (US Patent NO. 5, 262,311, published on November 16, 1993).

Regarding claims 7-9, 13, 160, and 286-288, since Penn *et al.,* teach that mRNA from a cell is used as a sample and Penn *et al.,* teach that mammalian cells contains approximately 15,000 different mRNA sequences (see column 1, third paragraph), Penn *et al.,* disclose that said plurality of different genes (from mRNA of a cell) consists of at least 100 to 10,000 different genes.

8. Claims 1, 4, 6, 11, 14-27, 31, 36, 45, 158, 161-174, 178, 180, and 289-292 are rejected under 35 U.S.C. 102(e) as being anticipated by Balaban *et al.,* (WO 01/081632 A1, priority date: April 25, 2000).

The rejection below is made in view of the ambiguity on claim 1 (see above rejections under 35 USC 112, second paragraph).

Regarding claims 1, 10, and 157, since Balaban *et al.,* teach a method for determining target sequence wherein said target sequence comprises a first sequence element joining a second sequence element comprising hybridizing said target sequence with a nucleic acid probe array comprising a set of probes for interrogating the joining sequence between said first sequence element and said second sequence element and obtaining information about the joining sequence based upon the hybridization of said target sequence with said set of probes wherein said first and second sequence elements are exons and said set of nucleic acid probes are immobilized on a substrate (see claims 11, 12, and 14 in pages 46 and 47, abstract, and pages 12 and 13), and mRNA is used as a sample (see page 14), and it is known that alternatively spliced mRNA variants are generated from using a different 3' or 5' splice junction of exons of pre-mRNA, Balaban *et al.,* disclose measuring the expression levels of a plurality of different individual exons or different individual multiexons in each of a plurality of different genes (ie., a plurality of exons of at least one gene) in the genome of an organism from which said cell sample is derived, wherein at least one gene in said plurality of different genes has an exon having a plurality of different variants, and wherein said measuring comprises measuring the expression level of each of said plurality of different variants of said exon in said at least one gene, each of

said plurality of different variants being a different splice form of said exon generated using a different 3' or 5' splice junction of said exon, thereby analyzing the exon expression of said cell sample as recited in claim 1, and disclose contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAs or nucleic acids, wherein said array comprises a plurality of polynucleotide probes of different nucleotide sequences (ie., a plurality of exon-specific probes) bound to different regions of a support, each of said different nucleotide sequences comprising a sequence complementary and hybridizable to a sequence in a different exon or multiexon of said cell sample, wherein said plurality of probes comprises probes that allow measurement of the expression levels of said plurality of different variants of said exon and measuring levels of hybridization between said probes and said RNAs or nucleic acids as recited in claim 10, and disclose contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAS or nucleic acids, wherein said array comprises a plurality of polynucleotide probes of different nucleotide sequences (ie., a plurality of exon-specific probes) bound to different regions of a support, each of said different nucleotide sequences comprising a sequence complementary and hybridizable to a sequence in a different exon or multiexon in the genome of an organism from which said cell sample is derived, wherein said plurality of probes comprises probes that allow measurement of the expression levels of said plurality of different variants of said exon and measuring levels of hybridization between said probes and said RNAS or nucleic acids as recited in claim 157.

Regarding claims 284 and 285, since Balaban *et al.*, teach a method for determining target sequence wherein said target sequence comprises a first sequence element joining a second sequence element comprising hybridizing said target sequence with a nucleic acid probe array comprising a set of probes for interrogating the joining sequence between said first sequence element and said second sequence element and obtaining information about the joining sequence based upon the hybridization of said target sequence with said set of probes wherein said first and second sequence elements are exons and said set of nucleic acid probes are immobilized on a substrate (see claims 11, 12, and 14 in pages 46 and 47, abstract ,and pages 12 and 13), and mRNA is used as a sample (see page 14), and it is known that alternatively spliced mRNA variants are generated from using a different 3' or 5' splice junction of exons of pre-mRNA, Balaban *et al.*, disclose contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAs or nucleic acids, wherein said array comprises (i) one or more exon specific probes comprising different nucleotide sequences for each of a plurality of different genes in the genome of said organism, each of said different nucleotide sequences being complementary and hybridizable to a sequence within a different individual exon; and (ii) a variant junction probe (ie., the exon probes with the sequence elements from the first and second exons) for each of a plurality of different variants of at least one exon, each of said variants being a different splice form of said exon generated using a different 3' or 5' splice junction of said exon, and each of said variant junction probes being a probe specific to a junction region of said variant and an adjacent exon in a multiexon comprising said variant of said exon, each of said exon specific probes and variant junction

probes being bound to a different region of a support, and measuring levels of hybridization between said probes and said RNAs or nucleic acids as recited in claim 284, and disclose contacting a positionally-addressable array of polynucleotide probes with a sample comprising RNAs or nucleic acids derived therefrom from said cell sample under conditions conducive to hybridization between said probes and said RNAs or nucleic acids, wherein said array comprises a plurality of junction specific probes (ie., the exon probes with the sequence elements from the first and second exon) comprising different nucleotide sequences for each of a plurality of different genes in the genome of said organism bound to different regions of a support, each of said different nucleotide sequences being complementary and hybridizable to a sequence spanning a junction region of a multiexon (ie., two exons), and wherein said plurality of junction specific probes comprises a variant junction probe for each of a plurality of different variants of at least one exon, each of said variants being a different splice form of said exon generated using a different 3' or 5' splice junction of said exon, and each of said variant junction probes being a probe specific to a junction region of said variant and an adjacent exon in a multiexon comprising said variant of said exon, and measuring levels of hybridization between said probes and said RNAs or nucleic acids as recited in claim 285.

Regarding claims 4, 6, 11, and 158, Balaban *et al.,* teach that said plurality of different individual exons or different individual multiexons consists of at least 2 to 3 different exons or multiexons (see Figure 1).

Regarding claims 158, 169-174, 280-283, and 289-292, Balaban *et al.,* teach that each of said different nucleotide sequences consists of 10 to 1,000 nucleotides (see claims 22-26 in pages 46 and 47).

Regarding claims 14-21 and 161-168, Balaban *et al.*, teach that said plurality of different genes consists of at least 100 to 50,000 different polynucleotide probes as recited in claims 14-17 and 161-164, and said positionally-addressable array has in the range of 100 to 50,000 different polynucleotide probes per 1 cm^2 as recited in claims 18-21 and 165-168 (see page 3, third paragraph and page 10, fourth paragraph).

Regarding claims 31 and 178, Balaban *et al.*, teach that at least one of said plurality of polynucleotide probes comprises a nucleotide sequence complementary and hybridizable to a multiexon as recited in claims 31 and 178 (see Figure 3).

Regarding claims 36 and 183, Balaban *et al.*, teach that said expression levels are measured as abundance of mRNA transcripts (see claim 11 in pages 45 and 46).

Regarding claim 45, Balaban *et al.*, teach that said organism is a human (see page 22, last paragraph bridging to page 23, first paragraph).

Therefore, Balaban *et al.*, teach all limitations recited in claims 1, 4, 6, 11, 14-27, 31, 36, 45, 158, 161-174, 178, and 289-292.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 86, 87, 89, 90, and 265 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penn *et al.,* as applied to claims 1, 4-6, 10-12, 22-32, 34, 36, 45, 157-159, 170-179, 181, 183, 264, 280-285, and 289-292 above, and further in view of Friend *et al.,* (US Patent No. 6,165,709, filed on February 26, 1998).

The teachings of Penn *et al.,* have been summarized previously, *supra.*

Penn *et al.,* do not disclose that said cell sample has been subjected to a perturbation as recited in claim 86 and comparing the expression levels of at least a portion of said plurality of different individual exons or different individual multiexons in said cell sample having been subjected to said perturbation with the expression level of said portion of said plurality of different individual exons or different individual multiexons in a cell sample of the same type not having been subjected to said perturbation as recited in claim 89 wherein said comparing comprises determining the difference between the expression level of each exon or multiexon in said portion of said plurality of different individual exons or different individual multiexons in said cell sample having been subjected to said perturbation and the expression level of corresponding exons or multiexons in said cell sample of the same type not having been subjected to said perturbation as recited in claim 90, and said perturbation is exposure to a drug

as recited in claim 265. However, Penn *et al.*, teach that said organism is a human as recited in claim 87 (see page 31, third paragraph).

Regarding claims 86, 89, 90, and 265, Friend *et al.*, teach transcript arrays for analyzing the transcriptional state in a cell, and especially for comparing the transcriptional states of two cells wherein a first cell that is exposed to a drug and a second cell that is not drug-treated. cDNA from two different cells are labeled with different fluorescence dyes and hybridized with a microarray with immobilized nucleic acid probes. When the drug treatment has no effect, either directly or indirectly, on the relative abundance of a particular mRNA in a cell, the mRNA levels are equally prevalent in both cells. When the drug treatment has an effect, either directly or indirectly, on the relative abundance of a particular mRNA in a cell, the ratio of the first fluorescence dye to the second fluorescence dye either increases or decreases (see columns 27-29 and 49-52).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 86, 89, 90, and 265 wherein said cell sample has been subjected to a perturbation and comparing the expression levels of at least a portion of said plurality of different individual exons or different individual multiexons in said cell sample having been subjected to said perturbation with the expression level of said portion of said plurality of different individual exons or different individual multiexons in a cell sample of the same type not having been subjected to said perturbation wherein said comparing comprises determining the difference between the expression level of each exon or multiexon in said portion of said plurality of different individual exons or different individual multiexons in said cell sample having been subjected to said perturbation and the

expression level of corresponding exons or multiexons in said cell sample of the same type not having been subjected to said perturbation and said perturbation is exposure to a drug in view of the prior art of Penn *et al.,* and Friend *et al.*. One having ordinary skill in the art has been motivated to do so because subjection of a cell sample to a perturbation such as a drug and determining the difference between the expression level of each exon or multiexon in a portion of said plurality of different individual exons or different individual multiexons in a cell sample having been subjected to said perturbation and the expression level of corresponding exons or multiexons in the cell sample of the same type not having been subjected to the perturbation would enhance to screen for compounds that have a desired effect on a cell and provide methods for drug development based on the methods for identifying drug targets (see Friend *et al.,* abstract and columns 1 and 2). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform the methods recited in claims 86, 87, 89, 90, and 265.

11. Claims 293-296 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penn *et al.,* as applied to claims 1, 4-6, 10-12, 22-32, 34, 36, 45, 157-159, 170-179, 181, 183, 264, 280-285, and 289-292 above, and further in view of DeRisi *et al.,* (Nature Genetics, 14, 457-460, 1996).

The teachings of Penn *et al.,* have been summarized previously, *supra.*

Penn *et al.,* do not disclose measuring the expression levels of at least 5 to1000 different variants in said plurality of different genes as recited in claims 293-296.

DeRisi *et al.,* teach to measure the expression levels of a plurality of different genes consisting of 870 different genes (see page 457, left column) and 870 different genes must include at least 870 different variants.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have measured the expression levels of at least 5 to 1000 different variants in said plurality of different genes as recited in claims 293-296 in view of the references of Penn *et al.,* and DeRisi *et al.*. One having ordinary skill in the art has been motivated to do so because optimization of numbers of measured different genes in a method for analyzing exon expression would have been obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to measure the expression levels of at least 5 to 1000 different variants in a plurality of different genes. Note that where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,713,257 B2. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but examined claims in this instant application are not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 in this instant application are not identical to claims 1-39 of U.S. Patent No. 6,713,257 B2, claims 1-39 of U.S. Patent No. 6,713,257 B2 are directed to the same subject matter and fall entirely within the scope of claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 in this instant application. In other words, claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 in this instant application are anticipated by claims 1-39 of U.S. Patent No. 6,713,257 B2.

14. Claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-114 and 177-184 of copending Application No. 10/813,506. An obviousness-type

double patenting rejection is appropriate where the conflicting claims are not identical, but examined claims in this instant application are not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 in this instant application are not identical to claims 1-114 and 177-184 of copending Application No. 10/813,506, claims 1-114 and 177-184 of copending Application No. 10/813,506 are directed to the same subject matter and fall entirely within the scope of claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 in this instant application. In other words, claims 1, 4-27, 29, 30, 36, 45, 157-175, 183, and 293-296 in this instant application are anticipated by claims 1-114 and 177-184 of copending Application No. 10/813,506.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. No claim is allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30

(November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)272-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
September 19, 2005

FRANK LU
PATENT EXAMINER